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Abstract: The core symptoms of schizophrenia spectrum disorders (SSD) include abnormal semantic processing which may rely on the ventral language stream of the human brain. Thus, structural disruption of the ventral language stream may play an important role in semantic deficits observed in SSD patients. Therefore, we compared white matter tract integrity in SSD patients and healthy controls using diffusion tensor imaging combined with probabilistic fiber tractography. For the ventral language stream, we assessed the inferior fronto-occipital fasciculus [IFOF], inferior longitudinal fasciculus, and uncinate fasciculus. The arcuate fasciculus and corticospinal tract were used as control tracts. In SSD patients, the relationship between semantic processing impairments and tract integrity was analyzed separately. Three-dimensional tract reconstructions were performed in 45/44 SSD patients/controls ("Bern sample") and replicated in an independent sample of 24/24 SSD patients/controls ("Basel sample"). Multivariate analyses of fractional anisotropy, mean, axial, and radial diffusivity of the left IFOF showed significant differences between SSD patients and controls (p(FDR-corr) < 0.001, $p2 = 0.23$) in the Bern sample. Axial diffusivity (AD) of the left UF was inversely correlated with semantic impairments ($r = -0.454$, p(FDR-corr) $= 0.035$). In the Basel sample, significant group differences for the left IFOF were replicated ($p < .01$, $p2 = 0.29$), while the correlation between AD of the left IFOF and semantic processing decline ($r = -0.376$, $p = .09$) showed a statistical trend. No significant effects were found for the dorsal language stream. This is direct evidence for the importance of the integrity of the ventral language stream, in particular the left IFOF, in semantic processing deficits in SSD.

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Anatomical integrity within the inferior fronto-occipital fasciculus and semantic processing deficits in schizophrenia spectrum disorders

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ABSTRACT

The core symptoms of schizophrenia spectrum disorders (SSD) include abnormal semantic processing which may rely on the ventral language stream of the human brain. Thus, structural disruption of the ventral language stream may play an important role in semantic deficits observed in SSD patients.

Therefore, we compared white matter tract integrity in SSD patients and healthy controls using diffusion tensor imaging combined with probabilistic fiber tractography. For the ventral language stream, we assessed the inferior fronto-occipital fasciculus [IFOF], inferior longitudinal fasciculus, and uncinate fasciculus. The arcuate fasciculus and corticospinal tract were used as control tracts. In SSD patients, the relationship between semantic processing impairments and tract integrity was analyzed separately. Three-dimensional tract reconstructions were performed in 45/44 SSD patients/controls ("Bern sample") and replicated in an independent sample of 24/24 SSD patients/controls ("Basel sample").

Multivariate analyses of fractional anisotropy, mean, axial, and radial diffusivity of the left IFOF showed significant differences between SSD patients and controls ($p_{(FDR\text{-}corr)}<0.001$, $\eta_p^2=0.23$) in the Bern sample. Axial diffusivity (AD) of the left UF was inversely correlated with semantic impairments ($r=-0.454$, $p_{(FDR\text{-}corr)}=0.035$). In the Basel sample, significant group differences for the left IFOF were replicated ($p<0.01$, $\eta_p^2=0.29$), while the correlation between AD of the left IFOF and semantic processing decline ($r=-0.376$, $p=0.09$) showed a statistical trend. No significant effects were found for the dorsal language stream.

This is direct evidence for the importance of the integrity of the ventral language stream, in particular the left IFOF, in semantic processing deficits in SSD.

KEY WORDS

Schizophrenia; First episode psychosis; Inferior frontooccipital fasciculus; Diffusion tensor imaging; Formal thought disorder; Semantic impairment.

INTRODUCTION

Since the introduction of the modern conceptualization of schizophrenia, formal thought disorder (TD) has been considered to be a core symptom of the disease (Bleuler, 1911; Kraepelin, 1919). Clinically, this corresponds to disturbances in oral communication. Particularly positive TD, such as semantic violations, seem to be highly disease-specific for schizophrenia spectrum disorders (SSD) (Kircher et al., 2018; Levy et al., 2010; Morgan et al., 2017; Salavera et al., 2013). Semantic anomalies have thus been incorporated into scales designed to assess TD, such as the Scale for the Assessment of Thought, Language and Communication (TLC) (Andreasen, 1979; Levy et al., 2010), and into general psychopathological scales devoted to psychotic syndromes, for example the Bern Psychopathology scale (BPS) (Strik et al., 2010).

Positive TD has been reported to be associated with structural alterations of the perisylvian language network of the brain, including the classic language areas of Wernicke and Broca (Fusar-Poli et al., 2012; Shepherd et al., 2012), as well as the middle longitudinal fasciculus (MLF) (Asami et al., 2013). However, the course and termination of the MLF in humans is still a matter of debate. Its role in language remains unclear (Champfleur et al., 2012; Maldonado et al., 2013). Indeed, increasing evidence indicates that language processing mainly relies on a dual-stream architecture, analogous to that of the visual system (Hickok and Poeppel, 2007, 2004; D. Saur et al., 2008; Ungerleider and Haxby, 1994): a dorsal phonological stream – including the arcuate fasciculus (AF) (Hickok and Poeppel, 2004) – and a ventral stream. The latter, linking the posteroinferior, occipitotemporal, part of the brain to the frontal lobe, depends on a direct pathway, the inferior fronto-occipital fasciculus (IFOF), and an indirect pathway, formed by the inferior longitudinal fasciculus (ILF) linked to the the uncinate fasciculus (UF) (Sarubbo et al., 2016). Functional disruption of the IFOF may well participate in verbal semantic processing disturbances: inhibitory electrical

stimulation of the IFOF during awake surgery induces semantic disturbances (Duffau et al., 2014) and reduced integrity of the left IFOF was found to correlate with subjects' semantic performance in healthy elderly (de Zubicaray et al., 2011) as well as brain-injured individuals (Han et al., 2013). This may also apply to TD within SDD. We therefore investigated the relationship between verbal semantic processing impairments and the integrity of the white matter (WM) integrity underlying language function in patients with schizophrenia and first episode psychosis (FEP) in two independent studies using diffusion tensor imaging (DTI). We hypothesized IFOF integrity is altered in patients with SSD and that semantic anomalies are correlated with these alterations.

PATIENTS AND METHODS

We retrieved preexisting data sets from the University Hospital of Psychiatry, Bern, Switzerland, and the Department of Psychiatry of the University of Basel, Switzerland. Detailed clinical and demographic characteristics of both SSD samples have been reported elsewhere (Schmidt et al., 2017, 2015; Stegmayer et al., 2017; Walther et al., 2017, 2015). Behavioral, perfusion and resting-state functional connectivity findings of the Bern sample (Schmidt et al., 2017, 2015; Stegmayer et al., 2017; Walther et al., 2017, 2015) and structural connectivity findings other than reported in the present manuscript of the Basel sample (Schmidt et al., 2017, 2015; Stegmayer et al., 2017; Walther et al., 2017, 2015) can be found in the referenced publications.

Participants

Patients and control subjects of the Bern sample

Thirty male and 15 female (total 45) schizophrenia patients and 26 male and 18 female (total 44) healthy control subjects matched for age and education were included in this study. Subjects were recruited from the inpatient and outpatient departments of the University Hospital of Psychiatry, Bern, Switzerland. Healthy controls were recruited among staff and via advertisements. All subjects were right-handed as determined by the Edinburgh handedness inventory (Oldfield, 1971). Exclusion criteria for both groups included current substance abuse or dependence other than nicotine; past or current medical or neurological conditions impairing movements, such as dystonia, idiopathic parkinsonism, and stroke; history of head trauma with concurrent loss of consciousness, and a history of electroconvulsive treatment. Exclusion criteria limited to control subjects were a history of any psychiatric disorder and any first-degree relatives with schizophrenia or schizoaffective disorder. All participants were interviewed with the Mini International Neuropsychiatric Interview (Sheehan et al., 1998) and the Comprehensive Assessment of Symptoms and History (Andreasen et al., 1992). Diagnoses were given according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria. All but 4 patients were under antipsychotic pharmacotherapy, and dosages were computed as chlorpromazine (CPZ) equivalents (Woods, 2003). Further assessment of schizophrenia psychopathology included

the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Demographic, global brain and clinical characteristics are given in Table 1. The study was approved by the local ethics committee and all participants provided written informed consent.

---------- please insert Table 1 about here ----------

Patients and control subjects of the Basel sample

Twenty-four patients with FEP and 24 healthy control subjects matched for age were included in this study. Subjects were recruited from the specialized outpatient clinic for early detection of psychosis at the Department of Psychiatry, University of Basel. As reported in Supplementary Table 3, most participants were right handers ($\chi^2_{(df=1)}$=0.76, p=0.67). Exclusion criteria for both groups included current substance abuse according to ICD-10 research criteria, history of previous psychotic disorder; psychotic symptomatology secondary to an organic disorder; psychotic symptomatology associated with an affective psychosis or a borderline personality disorder; age under 18 years; inadequate knowledge of the German language; and verbal IQ less than 70, measured with the German vocabulary test "Mehrfachwahl Wortschatz-Test Form B" (MWT-B) (Lehrl et al., 1995). Patients were further interviewed with the Basel Screening Instrument for Psychosis (BSIP) (Riecher-Rössler et al., 2008) and the Brief Psychiatric Rating Scale (BPRS) (Lukoff et al., 1986). All met the transition criteria of Young et al. (Yung et al., 1998). Only 9 patients received antipsychotics whose dosages were computed as CPZ equivalents (Woods, 2003). The study was also approved by the local ethics committee and all participants provided written informed consent.

Assessment of verbal semantic performance

Bern sample

Clinical data with respect to verbal semantic performance was retrieved from the following inventories (Table 1):

- BPS is a validated clinical rating scale developed to group psychotic symptoms in the domains of language, affectivity, and motor-behavior (Strik et al., 2010). The items *mistaking identity, coherence of speech, interruptions (including neologism), naming*

and apprehension of meaning were selected for the assessment of semantic processing.

- The TLC is a widely-used instrument for the assessment of language dysfunction (Goldberg et al., 1998). The items *semantic paraphasia, neologisms, word approximations, derailment, and incoherence* were selected for the assessment of semantic processing.

For the correlation of semantic impairments with measures of tract integrity, ten scales considered most representative for semantic processing (Levy et al., 2010) were selected (five from the BPS and five from TLC) and the values of these scales added up.

Basel sample

In the Basel sample, the available clinical tests were different from those of the Bern sample. Data relevant for verbal semantic performance were thus retrieved from the California verbal learning test (CVLT) (Woods et al., 2006) (see Supplementary Table 3). We used the List-Based Semantic Clustering Index of the CVLT (Stricker et al., 2002).

Image acquisition

At both sites, imaging was performed on a 3T MRI scanner (Bern: Siemens Magnetom Trio; Basel: Magnetom Verio, both Siemens Healthcare, Erlangen, Germany) with a 12-channel head coil for signal reception. 3D-T1-weighted images as well as DTI measurements were acquired. Technical details can be found in the Supplementary Methods.

Image processing

First, T1-weighted images were processed using the FreeSurfer software (http://surfer.nmr.mgh.harvard.edu/fswiki) (Dale et al., 1999; Fischl et al., 2004, 2002). We

used this tool to obtain the seed points needed for fiber tractography. The processing steps are described elsewhere (http://surfer.nmr.mgh.harvard.edu/fswiki/FreeSurferMethodsCitation). DTI data were then processed with the tracts constrained by underlying anatomy (TRACULA) toolbox (https://surfer.nmr.mgh.harvard.edu/fswiki/Tracula).

The TRACULA toolbox, which relies on a global probabilistic tractography approach with anatomical priors, was used for the automated reconstruction of a set of 18 major WM pathways from DTI images. Prior distributions on the neighboring anatomical structures of each pathway are derived from an atlas and combined with the FreeSurfer cortical parcellation scheme and subcortical segmentation to constrain the tractography solutions (Yendiki et al., 2014, 2011). In the present work, we focused on the specific set of the WM fiber tracts of interest named above, previously linked to semantic information processing in healthy subjects, i.e., the IFOF, UF and ILF (Friederici, 2009; Dorothee Saur et al., 2008) (Figure 1). For two control tracts, no effects were expected: we chose the arcuate fasciculus (AF) as a language-related tract which seems not to be involved in semantic processing (Friederici, 2009), as well as the corticospinal tract (CST) responsible for motor control of the extremities and no language function (Brodal and Walberg, 1982; Zarei et al., 2007). The probabilistic tractography is described in detail in the Supplementary Methods and the reconstructed tracts of interest are shown in Figure 1. For all tracts, fractional anisotropy (FA), axial diffusivity (AD), radial diffusivity (RD), and mean diffusivity (MD) values were extracted. Further details with respect to the TRACULA tractography toolbox and the output measures it provides can be found in the online documentation (https://surfer.nmr.mgh.harvard.edu/fswiki/Tracula) as well as in the relevant publications (Yendiki et al., 2016, 2014, 2011).

Statistical analysis

Comparisons of demographic and global brain measures as well as motion parameters across groups were performed using student's t-tests for independent samples and χ^2-Tests for gender and handedness. DTI-related measures (FA, AD, RD and MD) of the IFOF, ILF, UF as well as of the AF and CST (control tracts) were compared between groups using parametric univariate and multivariate analysis of covariance (ANCOVA and MANCOVA) models controlling for global diffusivity values. Because of the interdependency of the various DTI-derived measures, multivariate measures are more appropriate than univariate ones. We also tested whether the residuals after regressing out the global diffusivity measures were normally distributed using the Kolmogorov-Smirnov normality test. Almost all residuals were approximately normally distributed (Supplementary Table 1 and 2).

The associations between the DTI-related measures and semantic impairments were conducted using Spearman's rank order correlations based on residuals after regressing out global DTI-derived measures, age due to the wide age range (19-63 years) as well as gender, education, PANSS scores, and CPZ equivalents of the schizophrenia patients in the discovery (Bern) sample. Due to the smaller age range (18-41 years) in the FEP patients of the replication (Basel) sample, age was not regressed out. We also decided to not correct for gender, education, PANSS scores, and CPZ equivalents in the replication (Basel) sample because the sample size is very small (only 14 patients) so that adding additional covariates of no interest would reduce the number of degrees of freedom considerably and hence increasing the risk of false negative results.

Effect sizes are reported based on the correlation coefficient r (correlations) and η_p^2 (ANCOVA and MANCOVA). According to Cohen, effect sizes are denoted small if r=0.10 and η_p^2=0.01, moderate if r=0.30 and η_p^2=0.06, and large if r=0.50 and η_p^2=0.14. All tests were performed using IBM SPSS Statistics software version 25 (www.ibm.com/SPSS/Statistics). Error probability was set at $p<0.05$ and, if not otherwise

stated, two-tailed hypothesis testing has been performed. To account for the multiple comparisons performed, we applied the false discovery rate (FDR) correction. FDR correction was applied to the discovery (Bern) sample but not to the replication (Basel) sample. Given that results in the Basel data set are similar as those found with the Bern data set, the analyses of which are FDR corrected, the probability that the findings in the Basel data set represent false positives is very low, even if we do not correct the analyses of the Basel data set for multiple comparisons (Miller, 2009). For the group comparisons, we FDR corrected for the semantic-related tracts of interests (IFOF, ILF and UF) as well as for the language- and not semantic-related control tract (AF), but we did not FDR correct for the motor-related control tract (CST). Correlations have been performed only for the IFOF because the IFOF was the only tract for which we found a significant group difference with our MANCOVA models in both samples. In total, we FDR corrected for 52 statistical models, i.e., for the 32 ANCOVAs (4 measures x 4 tracts x 2 hemispheres), 12 MANCOVAs (4 tracts x left/right/both) as well as for the 8 Spearman correlations with semantic impairments (4 measures x 1 tract x 2 hemispheres). For the correlations in the replication sample, we used one-tailed hypothesis testing because of the anticipated direction of this association.

RESULTS

Demographic and global brain measures

Bern sample

There were no significant differences between schizophrenia patients and healthy controls with respect to sex, age, education, total intracranial volume, total gray matter volume, and total WM volume (t-tests for independent samples, all $p>0.19$, Table 1). The BPS and TLC scores are reported in Table 1.

DTI-derived global measures were significantly different between schizophrenia patients and healthy controls (Table 1 and Supplementary Results). Consequently, we used these global DTI measures as covariates-of-no-interest in our statistical models performed to investigate the integrity of the WM fiber pathways (see below).

With respect to head motion, no significant differences were found, neither for the translations and rotations nor for the dropout scores (all $p>0.12$) and the trend ($p=0.058$) in percent slices with poor resolution/image quality (slightly increased in patients) is neglectable due to the very small number of inadequate slices (less than 1% in both groups; Table 1). Note that most of the participants (79 out of 89, 88%) have zero percent bad slices rendering this variable not suitable for regression analysis and therefore we refrained from using percent bad slices as a covariate of no interest in our statistical models.

Basel sample

Patients with FEP and healthy controls did not differ in sex, handedness, age, total intracranial volume, total gray matter volume, and total white matter volume (all $p>0.15$, Supplementary Table 3). However, there was one statistically significant group difference regarding years of education that was higher in control subjects (Supplementary Table 3).

DTI-derived global measures were significantly different between groups. We therefore used these parameters as covariates-of-no-interest in our statistical models performed to investigate the integrity of the white matter fiber pathways.

With respect to head motion, no significant differences were found, neither for the translations, nor rotations, nor dropout scores, nor the percentage of inadequate slices (all $p>0.14$).

Group comparisons of WM fiber pathways

Bern sample

The reconstructed WM fiber pathways of interest (IFOF, ILF and UF) are shown in Figure 1 and the IFOF diffusivity values of the Bern sample (and that of the Basel sample as well) are listed in Supplementary Table 4.

---------- please insert Figure 1 about here ----------

Inferior fronto-occipital fasciculus

If considering the interdependency between the four diffusivity measures of the IFOF and applying the more appropriate MANCOVA model while correcting for the four global diffusivity measures, a robust and statistically significant difference between schizophrenia patients and healthy controls was found for the left and right IFOF together ($F_{(df=8,76)}=5.18$, $p_{(FDR\text{-}corrected)}=0.002$, $\eta_p^2=0.35$), as well as for the left IFOF ($F_{(df=4,80)}=5.87$, $p_{(FDR\text{-}corrected)}=0.009$, $\eta_p^2=0.23$), and for the right IFOF separately ($F_{(df=4,80)}=2.78$, $p=0.032$, $\eta_p^2=0.12$). The effect of the right IFOF lost statistical significance after FDR correction for multiple comparisons ($p_{(FDR\text{-}corrected}=0.19$). These effects were driven by decreased FA and increased AD, RD, and MD in patients compared to controls.

There were no significant group differences in any of the diffusivity measures (FA, AD, RD, and MD) when each measure was investigated in isolation while correcting for the corresponding global measure (ANCOVA).

Inferior longitudinal fasciculus, uncinate fasciculus, arcuate fasciculus and corticospinal tract

If all measures were analyzed simultaneously (MANCOVA), no significant group differences were found for almost all fiber bundles, except for the right AF ($F_{(df=6,78)}$=3.11, $p_{(FDR-corrected)}$=0.041, η_p^2=0.19).

When focusing on the four diffusivity measures of the tract center of the ILF, UF, AF, and CST, no significant group differences were found when analyzing each measure in isolation (ANCOVA), except for the right AF where patients showed increased AD compared to controls ($F_{(df=1,86)}$=6.09, p<0.05, η_p^2=0.066). Note that this effect is relatively weak compared with the ones reported for the IFOF, does not survive FDR correction ($p_{(FDR-corrected)}$=0.14), and it is restricted to the right non-language dominant hemisphere.

Basel sample

Inferior fronto-occipital fasciculus

If considering the interdependency between the four diffusivity measures of the IFOF and applying a MANCOVA model while correcting for the four global diffusivity measures, the same pattern of diffusivity differences as reported for the Bern sample emerged, except for the right IFOF: a strong and statistically significant difference between patients and healthy controls was found for the left and right IFOF together ($F_{(df=8,35)}$=2.68, p=0.021, η_p^2=0.38), for the left IFOF ($F_{(df=4,39)}$=3.89, p=0.009, η_p^2=0.29), but there was no significant group difference for the right IFOF ($F_{(df=4,39)}$=1.00, p=0.42, η_p^2=0.093).

In contrast to the Bern sample where univariate analyses did not reveal any significant effect of the four diffusivity measures, the left IFOF of the FEP patients of the Basel sample showed reduced FA ($F_{(df=1,45)}$=6.12, p=0.017, η_p^2=0.120), increased RD ($F_{(df=1,45)}$=6.30, p=0.016, η_p^2=0.123), and increased MD ($F_{(df=1,45)}$=4.77, p=0.034, η_p^2=0.096), whereas no effects were found for the right IFOF (FA: $F_{(df=1,45)}$=0.55, p=0.46, η_p^2=0.012; RD: $F_{(df=1,45)}$=0.35, p=0.56, η_p^2=0.008; MD: $F_{(df=1,45)}$=0.20, p=0.66, η_p^2=0.004). AD did not significantly differ for both IFOFs when each measure was investigated in isolation while correcting for the corresponding global measure (ANCOVA).

Inferior longitudinal fasciculus, uncinate fasciculus, arcuate fasciculus, and corticospinal tract

If all measures were analyzed simultaneously (MANCOVA), statistically significant differences between FEP patients and healthy controls were found for the left and right UF together ($F_{(df=6,37)}$=2.79, p=0.024, η_p^2=0.31), for the left UF ($F_{(df=3,40)}$=4.76, p=0.006, η_p^2=0.26), as well as the right ILF ($F_{(df=3,40)}$=3.75, p=0.018, η_p^2=0.22). For all other tracts, there were no statistically significant multivariate differences between the groups.

If focusing on the four diffusivity measures FA, AD, RD and MD of the tract center of the ILF, UF, AF, and CST no significant group differences were found when each measure was analyzed in isolation (ANCOVA).

Association of tract integrity with impairments in semantic processing

Bern sample

Semantic data were available for patients only. There were significant inverse correlations between semantic impairments and the diffusivity values (after regressing out the corresponding global diffusivity measure as well as age, sex, education, PANSS scores, and CPZ equivalents) of the left as well as right IFOF (see Table 2).

---------- please insert Table 2 about here ----------

The strongest inverse correlation was found between semantic impairments and AD of the left IFOF (r=-0.454, $p_{(FDR\text{-}corrected)}$=0.002), whereas semantic impairments and AD of the right IFOF were less strongly associated (r=-0.331, p=0.026) and did not survive correction for multiple comparisons ($p_{(FDR\text{-}corrected)}$=0.188) (scatterplots are shown in Figure 2). Beyond AD, MD of the left IFOF correlated also inversely with semantic impairments (r=-0.326, p=0.029). Note that the correlations of semantic impairments with AD of the right IFOF and that of MD of the left IFOF would not survive the FDR correction for multiple comparisons ($p_{(FDR\text{-}corrected)}$=0.188 and $p_{(FDR\text{-}corrected)}$=0.187, respectively). Moreover, the explained variance of the left IFOF (r^2=0.206) is about twice in magnitude than that of the right IFOF (r^2=0.110).

---------- please insert Figure 2 about here ----------

Basel sample

In order to correlate semantic impairments with measures of tract integrity, we selected the LBC of the CVLT. We report rank-ordered correlations (Spearman's rho) to safeguard against potential outliers in the semantic scores. These correlations are based on the residuals after regressing out the corresponding global diffusivity measure only. There was a significant correlation between the LBC and axial diffusivity in the left IFOF in the total sample of patients and controls (14 FEP patients and 18 controls, r=-0.317, p<0.05, see Supplementary Table 5), which was reduced to a statistical trend in the patient group only (14 FEP patients, r=-0.376, p=0.0925). Of note, the latter correlation is based on 14 patients only due to missing CVLT data in 10 patients. However, again, these correlations indicate greater semantic

impairments associated with reduced integrity of the left IFOF (scatterplots see in Supplementary Figure 1).

DISCUSSION

Compared to control subjects, schizophrenia and FEP patients in this investigation appear to have significantly structural alterations of the white matter tracts underlying semantic processing in the ventral language stream of the brain. While these structural, anatomical alterations have been previously described in FEP (Cheung et al., 2008; Epstein and Kumra, 2015; Lee et al., 2013; Lu et al., 2011; Melicher et al., 2015; Szeszko et al., 2008) and chronic schizophrenia (Boos et al., 2013; Schneiderman et al., 2009; Skelly et al., 2008), little was known about a potential functional correlate. Furthermore, a current study on tract specific age effects reported an abnormal maturation and accelerated aging for the IFOF (Cetin-Karayumak et al., 2019) as compared to controls. Again, whether these age-related group differences were associated with specific functional decline remains unanswered. Only recently, Viher et al. (Viher et al., 2018) reported a linear brain—behavior association between WM abnormalities in a predominantly left fronto-temporal language network and TD in schizophrenia. In that investigation, however, all fiber tracts of the ventral language stream (UF, ILF and IFOF) were combined. That investigation indicated that lower total FA was associated with increasing vulnerability to positive TD. Furthermore, Kubicki et al. (Kubicki et al., 2011) reported a correlation between semantic processing, as retrieved from several tests of language and verbal memory, and the ventral connectivity between the inferior frontal gyrus and the superior temporal gyrus in schizophrenia patients, also suggesting an implication of the ventral language stream in semantic processing problems in schizophrenia.

In the present investigation, AD changes within both the IFOFs' were negatively correlated with semantic processing impairment in schizophrenia patients ("Bern sample"). Although bilaterally significant, the effect sizes of the left IFOF are about twice as strong as the effect sizes in the right IFOF, both for group comparison and the correlation with semantic impairments. This correlation is in line with previous reports on similar anatomo-functional

correlations within language domains (Viher et al., 2018). This suggests that structural disintegration of white matter pathways can indeed be interpreted as representative of the corresponding functional decline. Severity of schizophrenia psychopathology, however, as represented by the PANSS scores, does not correlate statistically significantly with AD, neither for the left nor for the right IFOF. With a trend towards statistical significance, the observed negative correlation between anatomical integrity and semantic performance was reproduced in our replication sample ("Basel sample"). In addition, in the latter, when anatomofunctional correlations are computed across FEP patients and healthy controls, the correlation between semantic processing impairment and AD changes becomes significant for the left (but not the right) IFOF. A left side's predominance of the IFOF in verbal semantic processing is generally supported by data from intraoperative direct electrostimulation and semantic performance in healthy elderly individuals (Duffau et al., 2014). Compared to healthy controls FEP patients' in this investigation exhibit significant structural alterations in the left, but not the right IFOF. With regard to schizophrenia patients, the same difference emerged for both the left and the right IFOF. This observation might represent a compensatory mechanism seen in FEP and lost in chronic SSD. On the other hand, progressive bilateral structural alteration related to verbal semantic processing, exhibiting the same left-sided predominance, could also explain these findings.

The present study indicates that the involvement of the IFOF with respect to semantic processing is selective in patients suffering from confirmed psychotic illness: There are no significant correlations for the AF in neither the Bern nor the Basel sample. Concerning the ILF we found a negative correlation for the FA on the right in the Bern sample, which lose significance after FDR correction. With regard to the Basel sample there is a correlation between semantic processing decline and AD of the left and right UF. However, when

anatomofunctional correlations are computed across FEP patients and healthy controls, the correlation remains significant only for the right non-language dominant UF.

The isolated correlation of semantic decline and anomalies in AD, not reflected by other DTI measures, might appear surprising. While the majority of DTI studies in schizophrenia have shown decreased FA in long-range association tracts, alterations in the radial or axial diffusivity have attracted less attention until now (Koch et al., 2013). Isolated AD abnormalities have been interpreted as a preliminary stage before more severe changes (Qiu et al., 2008; Zivadinov et al., 2013) and were attributed among others to possible changes in axonal number, size or compactness (Harsan et al., 2006; Schonberger et al., 2006; Song et al., 2003). Such changes in AD, without FA anomalies have been observed within the ventral and dorsal language systems of nonpsychotic high risk patients—with high risk subjects demonstrating a deviation from the normal maturation trajectory (Kubicki et al., 2013). These changes might indeed precede further pathway pathologies (including myelin changes) (Kubicki et al., 2013). Nevertheless, neuroanatomical correlates of AD changes are still under investigation and conflicting results are reported for AD changes (Zikou et al., 2016).

The retrospective nature and the relatively small size of the control (Basel) sample limit the interpretation of the present investigation. In order to gain more precise insight into the anatomical correlates of semantic processing alterations in SSD, broader prospective data are needed. Finally, in the scatterplots of Figure 2, the amount of "zeros" is explained by the absence of clinically apparent semantic impairments in more than half of the patients (23 out of 45) in the Bern sample. Nevertheless, (1) in the Basel sample, where no such "zeros" occurred, a similar association has been found; (2) most schizophrenia patients with no semantic impairments showed positive residual AD values in the IFOF, whereas the patients with semantic impairments showed negative residual AD values in the IFOF, (3) even if

statistical significance is lost due to lack of power, the direction of the correlation remains the same when excluding the 23 patients with no semantic impairments, and (4) when using the mean of all BPS and TCS scales instead of the mean of only the semantic related scales, there is still an inverse relationship although almost all “zeros” disappeared.

CONCLUSION

Structural alterations of the IFOF correlate with patients' semantic processing impairments in schizophrenia spectrum disorders. This is the first direct evidence for a contribution of disrupted IFOF integrity to semantic processing deficits in these patients.

FIGURE CAPTIONS

Figure 1 **White matter pathways investigated in the present study.** DTI data processed with TRACULA reveals the three major white matter pathways of the ventral language processing stream, i.e., the inferior fronto-occipital fasciculus (IFOF, in red), inferior longitudinal fasciculus (ILF, in blue) and the uncinate fasciculus (UF, in green). The arcuate fasciculus and corticospinal tract (not shown) served as controls. A. right lateral view; B. left lateral view; C. inferior view; D. superior view; E. anterior view; F. posterior view.

Figure 2 **Associations between semantic processing impairments and axial diffusivity of the inferior fronto-occipital fasciculus (IFOF).** Scatterplots of the correlations between semantic processing impairments and the axial diffusivity standardized residuals (after regressing out the effects of global axial diffusivity, age, sex, education, PANSS score, and CPZ equivalents) of the left IFOF ($r = -0.454$, $p_{(FDR\text{-}corrected)} = 0.035$, upper panel) and the right IFOF ($r = -0.331$, $p_{(FDR\text{-}corrected)} = 0.188$, lower panel). Abbreviations: CPZ, chlorpromazine; IFOF, inferior fronto-occipital fasciculus; PANSS, positive and negative symptom scale.

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Table 1. Demographic, global brain and clinical characteristics of the schizophrenia patients and healthy control subjects of the Berne sample.

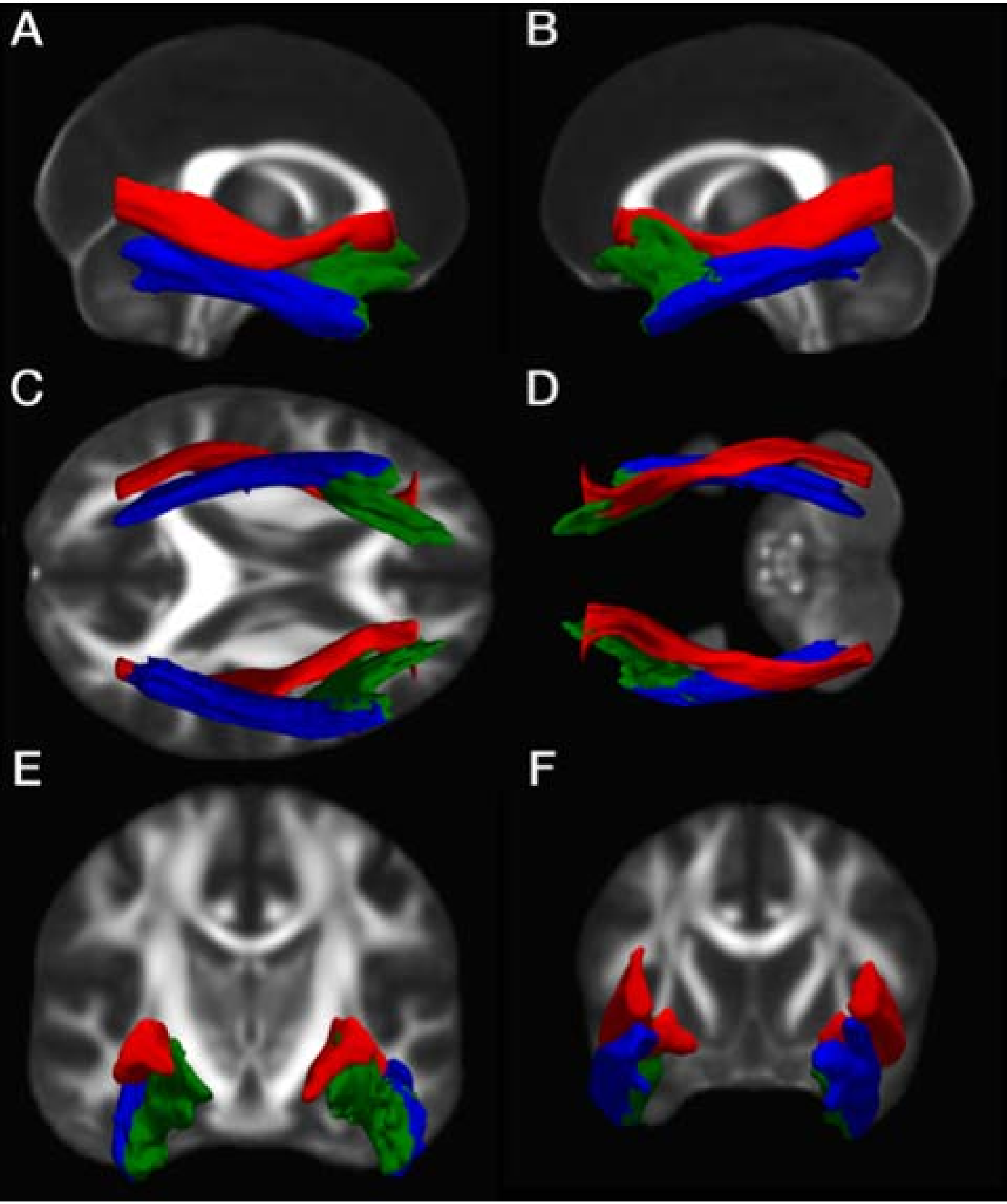
	Schizophrenia (n = 45)				Control subjects (n = 44)						
Measures	**Mean**	**SD**	**Min.**	**Max.**	**Mean**	**SD**	**Min.**	**Max.**	**t-value**	**df**	**p**
Age (years)	38.1	11.5	19.0	63.0	38.8	13.6	18.0	64.0	0.26	84.1	0.79
Education (years)	13.5	3.1	8.0	21.0	14.1	2.7	8.0	20.0	1.10	87.0	0.27
Duration of illness (years)	12.0	12.4	0.0	45.1	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Number of episodes	6.4	7.1	1.0	30.0	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Total intracranial volume (liter)	1.553	0.159	1.212	1.903	1.550	0.149	1.307	1.907	-0.11	87.0	0.91
Total gray matter volume (liter)	0.619	0.081	0.424	0.806	0.639	0.057	0.548	0.788	1.33	79.2	0.19
Total white matter volume (liter)	0.453	0.057	0.307	0.584	0.460	0.060	0.347	0.590	0.59	87.0	0.56
Average fractional anisotropy (0-1)	0.275	0.013	0.248	0.309	0.278	0.010	0.261	0.301	1.52	82.0	0.13
Average axial diffusivity (mm^2/s)	0.0012	0.00007	0.0011	0.0014	0.0012	0.00005	0.0011	0.0013	-1.95	78.4	0.054
Average radial diffusivity (mm^2/s)	0.0008	0.00006	0.0007	0.0010	0.0008	0.00004	0.0007	0.0009	-2.72	74.3	0.008
Average mean diffusivity (mm^2/s)	0.0010	0.00007	0.0009	0.0011	0.0009	0.00005	0.0008	0.0010	-2.07	78.7	0.042
Average motion translation (mm)	1.523	0.359	0.938	2.382	1.513	0.335	0.793	2.250	-0.13	87.0	0.90
Average motion rotation (degree)	0.007	0.0023	0.003	0.013	0.006	0.0023	0.002	0.012	-1.55	87.0	0.12
Percent bad slices	0.022	0.0565	0.0	0.29	0.0043	0.0222	0.00	0.14	-1.94	57.5	0.058
Average dropout scores	1.032	0.091	1.00	1.44	1.011	0.058	1.00	1.37	-1.30	75.2	0.20
Bern Psychopathology Scale[A]	4.09	3.43	0.0	13.0	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Thought, Language, and Communication	6.16	7.25	0.0	29.0	N/A	N/A	N/A	N/A	N/A	N/A	N/A
PANSS (sum of positive symptoms)	18.3	6.41	7.0	33.0	N/A	N/A	N/A	N/A	N/A	N/A	N/A
PANSS (sum of negative symptoms)	18.3	4.94	10.0	35.0	N/A	N/A	N/A	N/A	N/A	N/A	N/A
PANSS (sum of total symptoms)	72.8	17.4	40.0	112.0	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Frequency				**Frequency**				χ^2	**df**	**p**
Sex (male / female)	30 / 15				26 / 18				0.55	1	0.52

All measures were compared between groups using student's t-tests for independent samples. [A]Negative values (-1) were converted to positive values (1) to compute the sum of each patient. Abbreviations: df, degrees of freedom; Max., maximum; Min., minimum; N/A, not available; p, p-value; PANSS, positive and negative symptom scale; SD, standard deviation.

Table 2. Correlations between semantic processing impairments and measures of tract integrity within the schizophrenia patients of the Berne sample.

		Fractional anisotropy	Axial diffusivity	Radial diffusivity	Mean diffusivity
IFOF left	Spearman's rho	-0.048	**-0.454**	-0.214	-0.326
	p-value (FDR-corr.)	0.935	**0.035**	0.519	0.187
IFOF right	Spearman's rho	-0.054	-0.331	-0.196	-0.281
	p-value (FDR-corr.)	0.935	0.188	0.569	0.288

Partial Spearman rank-ordered correlations corrected for the effects of global diffusivity measures, age, sex, education, PANSS scores, and CPZ equivalents. Significant correlations are printed in bold. Abbreviations: FDR-corr., false discovery rate corrected; CPZ, chlorpromazine; IFOF, inferior fronto-occipital fasciculus; PANSS, positive and negative symptom scale.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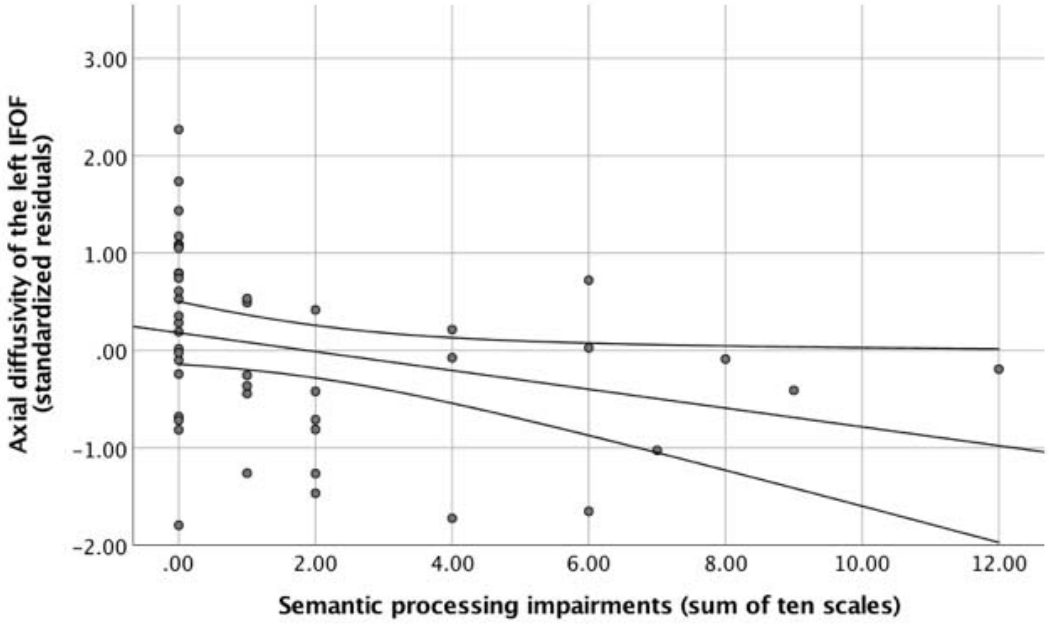
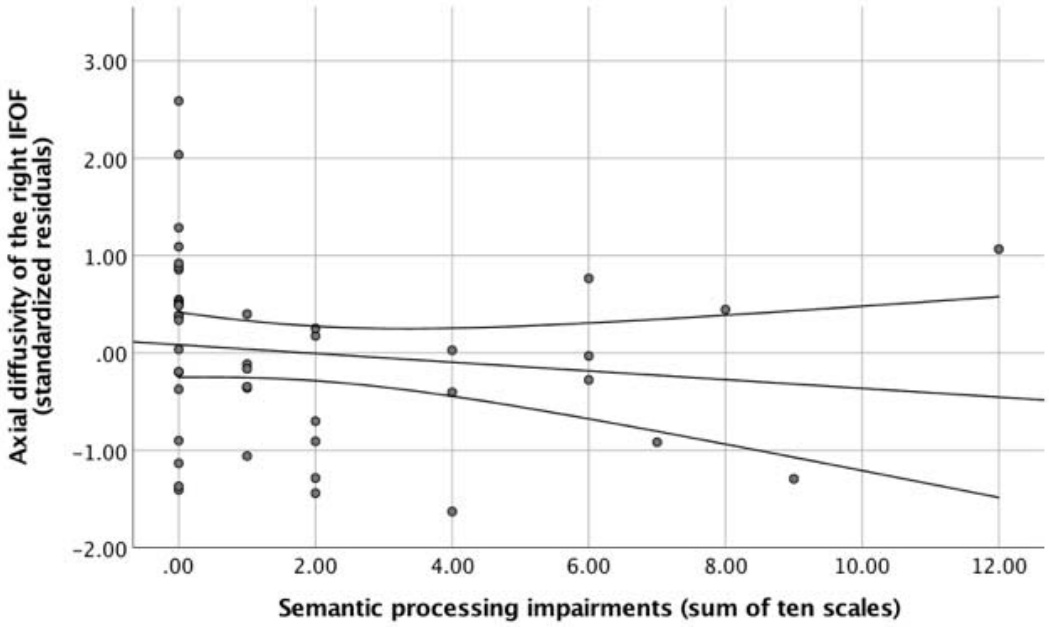

Axial diffusivity of the left IFOF (standardized residuals)
3.00
2.00
1.00
.00
-1.00
-2.00
.00
2.00
4.00
6.00
8.00
10.00
12.00
Semantic processing impairments (sum of ten scales)


Axial diffusivity of the right IFOF (standardized residuals)
3.00
2.00
1.00
.00
-1.00
-2.00
.00
2.00
4.00
6.00
8.00
10.00
12.00
Semantic processing impairments (sum of ten scales)

Supplemental Material

SUPPLEMENTARY METHODS

Image acquisition

Bern sample

Imaging was performed on a 3T MRI scanner (Siemens Magnetom Trio, Siemens Healthcare, Erlangen, Germany) with a 12-channel radio frequency head coil for signal reception. 3D-T1-weighted (Modified Driven Equilibrium Fourier Transform Pulse Sequence; MDEFT) (1) images for each subject have been obtained, providing 176 sagittal slices with 256x256 matrix points with a non-cubic field of view (FOV) of 256 mm, yielding a nominal isotopic resolution of 1 mm^3 (i.e., 1x1x1 mm). Further scan parameters for the anatomical data were 7.92 ms repetition time (TR), 2.48 ms echo time (TE), 900 ms inversion time (TI) and a flip angle $\alpha = 16°$.

For diffusion tensor imaging (DTI) measurements, we used a spin echo planar imaging (EPI) sequence (59 slices, FOV = 256x256 mm^2, sampled on a 128x128 matrix, slice thickness = 2 mm, gap between slices = 0 mm, resulting in 2 mm^3 isotopic voxel resolution) and TR/TE = 8,000/92 ms covering the whole brain (40 mT/m gradient, 6/8 partial Fourier, GRAPPA factor 2, bandwidth 1346 Hz/Px). Diffusion-weighted images (DWI) were positioned in the axial plane parallel to the AC-PC line and measured along 42 directions with a b-value = 1,300 s/mm^2. The sequence included 4 images without diffusion weighting (e.g. b-value = 0 s/mm^2; the first and every subsequent 12^{th} image). We used a balanced and rotationally invariant diffusion-encoding scheme over the unit sphere to generate the DTI data. Acquisition time was 6 min.

Basel sample

Imaging was performed on a 3T MRI scanner (Magnetom Verio, Siemens Healthcare, Erlangen, Germany). DTI data were acquired during 10 minutes, based on a single-shot echo planar imaging sequence with the following parameters: echo TE/TR = 95/9,200 ms, FOV = 320 mm and 54 axial slices of 2.5 mm slice thickness covering the whole brain with an in-plane resolution of 2.5 x 2.5 mm^2. In addition, a 12-channel radio frequency head coil was used, as well as GRAPPA parallel imaging with an acceleration factor of 2, with phase partial Fourier of 6/8. In total, 30 isotropically distributed diffusion weighted directions with b-values of b = 900s/mm^2 and one single reference image with b = 0s/mm^2 were acquired twice as two averages.

In addition, a high-resolution T1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE) image was acquired (TR = 2,000 ms; TE = 3.37 ms; flip angle = 8°; inversion time = 1,000 ms; 176 slices; slice thickness = 1 mm; voxel size = 1 x 1 x 1mm3).

Image processing

First, T1-weighted images were processed using the FreeSurfer software suite (http://surfer.nmr.mgh.harvard.edu/fswiki), which is originally designed to perform surface-based morphometry (2–4). We used this tool to obtain the seed points needed for fiber tractography. The processing steps are described elsewhere (http://surfer.nmr.mgh.harvard.edu/fswiki/FreeSurferMethodsCitation). DTI data were then processed with the tracts constrained by underlying anatomy (TRACULA) toolbox (https://surfer.nmr.mgh.harvard.edu/fswiki/Tracula).

The TRACULA toolbox, which relies on a global probabilistic tractography approach with anatomical priors, was used for the automated reconstruction of a set of 18 major WM pathways from DTI images. Prior distributions on the neighboring anatomical structures of each pathway are derived from an atlas and combined with the FreeSurfer cortical parcellation scheme and subcortical segmentation to constrain the tractography solutions (5,6). In the present work, we focused on a specific set of the WM fiber tracts of interest that have previously been linked to semantic information processing in healthy subjects, namely the IFOF, UF and ILF (7,8) (Figure 1). We also investigated two control tracts, for which no effects have been expected. We choose the arcuate fasciculus (AF) as a language-related tract, which seems not to be involved in semantic processing (7) as well as the corticospinal tract (CST) that is related to the motor control of the extremities (9,10). It is important to note that in the framework of the TRACULA tractography toolbox, the AF is denoted as the temporal part of the superior longitudinal fasciculus (see page 3 of (6)). Further details with respect to the TRACULA tractography toolbox and the output measures it provides can be found in the online documentation (https://surfer.nmr.mgh.harvard.edu/fswiki/Tracula) as well as in the relevant publications (5,6,11). The IFOF, however, is not among the 18 WM fiber tracts provided by TRACULA and therefore we tracked the IFOF separately based on the same TRACULA processed DTI data, but used seed and target regions of interest (ROIs) as described in the literature (12). Two ROIs were created according to guidelines described on p. 637 and delineated in Fig. 8 on p. 638 of the study by Wakana and colleagues. For the first ROI, a coronal slice was identified at the middle point between the posterior edge of the cingulum and the posterior edge of the parieto-occipital sulcus and for the second ROI, a coronal slice is selected at the anterior edge of the genu of corpus callosum and the entire hemisphere is delineated (12). Both cingulate gyri and both thalami were used as exclusion masks to avoid spurious fibers running into these two brain structures (12). The masks for the cingulate gyri and thalami were derived from the Harvard-Oxford cortical and subcortical structural atlas, respectively (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases).

Using the IFOF ROIs constructed as described by Wakana and colleagues as well as the exclusion mask containing the thalami and cingulate gyri, tracking was performed in both directions. Once the first ROI was used as seed mask and the second ROI as waypoint and termination mask and once the second ROI was used as seed mask and the first ROI as waypoint and termination mask because probabilistic tractography is in contrast to deterministic tractography not symmetric (13). Further details about the probabilistic tractography steps can be found here (http://surfer.nmr.mgh.harvard.edu/fswiki/trac-all) and here (http://surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial/Tracula). Default tracking parameters were applied as described elsewhere (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDT/UserGuide#BEDPOSTX).

Resulting tracts were in MNI space. After fiber tractography, within-tract probabilistic values were normalized at the individual level by dividing the number of streamlines passing through each voxel by the total number of obtained streamlines ("waytotal")(13). Subsequently, normalized tracts were set at a threshold of 0.01 incorporating only those voxels where at least 1% of the total number of streamlines passed. Final tracts were binarized and back-transformed from MNI into subject's native space using inverse linear and nonlinear transformation and were used as subject-specific masks for extraction of fractional anisotropy (FA), axial diffusivity (AD), radial diffusivity (RD) and mean diffusivity (MD) values from the corresponding diffusivity maps using FSL's functions "fslstats" and "fslmaths".

Note that for tracts other than the IFOF, i.e., for the ILF, UF, AF and the CST, we used the diffusivity measure averaged across the tract center as the measure of interest because this measure is most comparable with the thresholded diffusivity measure used for the IFOF.

In order to exclude biased diffusivity values due to head movement between groups, four automated measures of motion were derived from TRACULA (5), including average volume-by-volume translation, average volume-by-volume rotation, percentage of slices with signal drop-out, and signal drop-out severity (Table 1 for the Bern sample and Supplementary Table 3 for the Basel sample).

SUPPLEMENTARY RESULTS

Demographic and global brain measures

Bern sample

There were no significant differences between schizophrenia patients and healthy controls with respect to sex, age, education, total intracranial volume, total gray matter volume, and total WM volume (t-tests for independent samples, all $p > 0.19$, see Table 1).

With respect to the DTI-derived global measures, while there was no difference in global FA between groups ($p = 0.13$), there was a trend towards increased global AD in schizophrenia patients relative to healthy controls ($p = 0.054$) and global RD and MD values were significantly increased in patients

compared with controls ($p < 0.01$ and $p < 0.05$, respectively). Consequently, we used these DTI measures as covariates of no interest in our statistical models performed to investigate the integrity of the WM fiber pathways (see below).

With respect to head motion, no significant differences have been found, neither for the translations and rotations nor for the dropout scores (all $p > 0.12$) and the trend ($p = 0.058$) in percent slices with poor resolution/image quality (slightly increased in patients) may be neglected due to the small number of bad slices (less than 1% in both groups; Table 1).

Basel sample

Patients with FEP and healthy controls did not differ in sex, handedness, age, total intracranial volume, total gray matter volume, and total white matter volume (all $p > 0.15$, see Supplementary Table 1). However, there was a significant group difference regarding years of education (see Supplementary Table 1).

With respect to the DTI-derived global measures, there were significant difference in global FA between groups ($p = 0.031$), statistical trends towards differences in global MD and RD ($p = 0.057$ and $p = 0.065$, respectively), whereas global AD was not significantly different between groups ($p = 0.10$). Therefore, we used these parameters as covariates of no interest in our statistical models performed to investigate the integrity of the white matter fiber pathways.

With respect to head motion, no significant differences have been found, neither for the translations, rotations nor for the dropout scores and percent bad slices (all $p > 0.14$).

SUPPLEMENTARY RESULTS

Supplementary Table 1. Normal distribution of the data of the Bern sample. Shown are results of the Kolmogorov-Smirnov test based on the residual values after regression out (multivariate as well as univariate) the effects of the global diffusivity measures.

	Fiber Tracts									
Residuals	**IFOF**		**ILF**		**UF**		**AF**		**CST**	
Multivariate-corrected	**Statistic[a]**	**p-value**	**Statistic[a]**	**p-value**	**Statistic[a]**	**p-value**	**Statistic[a]**	**p-value**	**Statistic[a]**	**p-value**
FA left (df = 89)	0.062	0.200*	0.056	0.200*	0.137	0.0003	0.067	0.200*	0.056	0.200*
AD left (df = 89)	0.047	0.200*	0.091	0.068	0.080	0.200*	0.056	0.200*	0.062	0.200*
RD left (df = 89)	0.072	0.200*	0.076	0.200*	0.088	0.083	0.056	0.200*	0.047	0.200*
MD left (df = 89)	0.072	0.200*	0.073	0.200*	0.070	0.200*	0.052	0.200*	0.069	0.200*
FA right (df = 89)	0.054	0.200*	0.086	0.099	0.077	0.200*	0.070	0.200*	0.059	0.200*
AD right (df = 89)	0.079	0.200*	0.073	0.200*	0.072	0.200*	0.060	0.200*	0.091	0.066
RD right (df = 89)	0.082	0.198	0.081	0.200*	0.122	0.002	0.077	0.200*	0.128	0.001
MD right (df = 89)	0.089	0.079	0.060	0.200*	0.058	0.200*	0.109	0.011	0.171	<0.0001
Univariate-corrected	**Statistic[a]**	**p-value**	**Statistic[a]**	**p-value**	**Statistic[a]**	**p-value**	**Statistic[a]**	**p-value**	**Statistic[a]**	**p-value**
FA left (df = 89)	0.064	0.200*	0.050	0.200*	0.125	0.002	0.084	0.165	0.064	0.200*
AD left (df = 89)	0.051	0.200*	0.082	0.194	0.103	0.022	0.052	0.200*	0.058	0.200*
RD left (df = 89)	0.060	0.200*	0.078	0.200*	0.115	0.006	0.044	0.200*	0.089	0.079
MD left (df = 89)	0.061	0.200*	0.071	0.200*	0.090	0.069	0.074	0.200*	0.077	0.200*
FA right (df = 89)	0.098	0.036	0.103	0.021	0.085	0.155	0.063	0.200*	0.064	0.200*
AD right (df = 89)	0.077	0.200*	0.071	0.200*	0.064	0.200*	0.076	0.200*	0.079	0.200*
RD right (df = 89)	0.067	0.200*	0.048	0.200*	0.095	0.048	0.070	0.200*	0.111	0.009
MD right (df = 89)	0.078	0.200*	0.063	0.200*	0.086	0.105	0.095	0.046	0.149	<0.0001

a Lilliefors Significance Correction. * This is a lower bound of the true significance. Significant deviations from normal distribution are in red. Abbreviations: AD, axial diffusivity; AF, arcuate fasciculus; CST, corticospinal tract; FA, tractional anisotropy; IFOF, fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; MD, mean diffusivity; RD, radial diffusivity; UF, uncinate fasciculus.

Supplementary Table 2. Normal distribution of the data of the Basel sample. Shown are results of the Kolmogorov-Smirnov test based on the residual values after regression out (multivariate as well as univariate) the effects of the global diffusivity measures.

	Fiber Tracts									
Residuals	**IFOF**		**ILF**		**UF**		**AF**		**CST**	
Multivariate-corrected	**Statistic[a]**	**p-value**	**Statistic[a]**	**p-value**	**Statistic[a]**	**p-value**	**Statistic[a]**	**p-value**	**Statistic[a]**	**p-value**
FA left (df = 48)	0.086	0.200*	0.098	0.200*	0.127	0.052	0.120	0.083	0.080	0.200*
AD left (df = 48)	0.110	0.195	0.06	0.200*	0.055	0.200*	0.098	0.200*	0.083	0.200*
RD left (df = 48)	0.111	0.179	0.088	0.200*	0.068	0.200*	0.073	0.200*	0.085	0.200*
MD left (df = 48)	0.123	0.066	0.089	0.200*	0.086	0.200*	0.083	0.200*	0.086	0.200*
FA right (df = 48)	0.079	0.200*	0.064	0.200*	0.075	0.200*	0.076	0.200*	0.100	0.200*
AD right (df = 48)	0.093	0.200*	0.067	0.200*	0.080	0.200*	0.140	0.020	0.097	0.200*
RD right (df = 48)	0.146	0.012	0.102	0.200*	0.092	0.200*	0.089	0.200*	0.080	0.200*
MD right (df = 48)	0.125	0.060	0.132	0.035	0.086	0.200*	0.086	0.200*	0.061	0.200*
Univariate-corrected	**Statistic[a]**	**p-value**	**Statistic[a]**	**p-value**	**Statistic[a]**	**p-value**	**Statistic[a]**	**p-value**	**Statistic[a]**	**p-value**
FA left (df = 48)	0.080	0.200*	0.099	0.200*	0.125	0.059	0.079	0.200*	0.083	0.200*
AD left (df = 48)	0.083	0.200*	0.105	0.200*	0.097	0.200*	0.075	0.200*	0.088	0.200*
RD left (df = 48)	0.091	0.200*	0.061	0.200*	0.124	0.064	0.061	0.200*	0.087	0.200*
MD left (df = 48)	0.075	0.200*	0.105	0.200*	0.153	0.007	0.065	0.200*	0.094	0.200*
FA right (df = 48)	0.069	0.200*	0.064	0.200*	0.064	0.200*	0.122	0.070	0.104	0.200*
AD right (df = 48)	0.080	0.200*	0.142	0.017	0.071	0.200*	0.096	0.200*	0.060	0.200*
RD right (df = 48)	0.158	0.004	0.089	0.200*	0.075	0.200*	0.115	0.139	0.066	0.200*
MD right (df = 48)	0.125	0.058	0.103	0.200*	0.109	0.200*	0.100	0.200*	0.071	0.200*

a Lilliefors Significance Correction. * This is a lower bound of the true significance. Significant deviations from normal distribution are in red.
Abbreviations: AD, axial diffusivity; AF, arcuate fasciculus; CST, corticospinal tract; FA, tractional anisotropy; IFOF, fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; MD, mean diffusivity; RD, radial diffusivity; UF, uncinate fasciculus.

Supplementary Table 3. Demographic, global brain and clinical characteristics of the schizophrenia spectrum disorders patients and healthy control subjects from the Basel sample.

	First episode psychosis (n = 24)				Control subjects (n = 24)						
Measures	**Mean**	**SD**	**Min.**	**Max.**	**Mean**	**SD**	**Min.**	**Max.**	**t-value**	**df**	**p**
Age (years)	26.0	7.1	18.3	40.6	27.3	4.6	19.0	39.0	0.84	38.8	0.45
Education (years)	13.2	2.9	7.0	19.0	15.4	2.9	9.0	23.0	2.59	46.0	0.013
Total intracranial volume (liter)	1.656	0.172	1.261	1.994	1.611	0.153	1.392	1.877	-0.95	46.0	0.35
Total gray matter volume (liter)	0.709	0.064	0.557	0.825	0.687	0.061	0.583	0.813	-1.25	46.0	0.22
Total white matter volume (liter)	0.480	0.062	0.338	0.603	0.464	0.049	0.385	0.574	-0.99	46.0	0.33
Average fractional anisotropy (0-1)	0.249	0.012	0.227	0.275	0.243	0.007	0.229	0.257	-2.24	38.0	0.031
Average axial diffusivity (mm^2/s)	0.0012	0.00005	0.0012	0.0013	0.0013	0.00004	0.0012	0.0013	1.67	46.0	0.10
Average radial diffusivity (mm^2/s)	0.0009	0.00005	0.0008	0.0010	0.0009	0.00004	0.0008	0.0010	1.95	46.0	0.057
Average mean diffusivity (mm^2/s)	0.0010	0.00005	0.0009	0.0011	0.0010	0.00004	0.0010	0.0011	1.98	46.0	0.065
Average motion translation (mm)	1.255	0.439	0.667	2.397	1.201	0.367	0.647	2.013	-0.46	46.0	0.65
Average motion rotation (degree)	0.011	0.005	0.006	0.028	0.010	0.004	0.004	0.018	-1.50	46.0	0.14
Percent bad slices	0.029	0.106	0.00	0.52	0.002	0.007	0.00	0.04	-1.26	23.2	0.22
Average dropout scores	1.009	0.024	1.00	1.10	1.025	0.124	1.00	1.61	0.64	24.7	0.53
MWT-B[A]	106.7	16.5	80.0	134.0	N/A	N/A	N/A	N/A	N/A	N/A	N/A
BPRS	44.5	12.9	15.0	72.0	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Semantic LBC of the CVLT[B]	1.86	2.01	-0.40	6.64	3.12	2.66	-1.88	7.32	1.52	30.0	0.14
	Frequency				**Frequency**				**χ^2**	**df**	**p**
Sex (male / female)	16 / 8				10 / 14				3.02	1	0.15
Handedness (right / left)	20 / 4				22 / 2				0.76	1	0.67

All measures were compared between groups using student's t-tests for independent samples. [A]based on n = 19. [B]based on n = 14 patients and n = 18 control subjects. Abbreviations: BPRS, Brief Psychiatric Rating Scale; χ^2, Chi square; CVLT, California verbal learning test; df, degree of freedom; LBC, list-based semantic clustering index; Max., maximum; Min., minimum; mm, millimeter; MWT-B, Mehrfachwahl-Wortschatztest; n, number of participants; p, p-value; s, second; SD, standard deviation.

Supplementary Table 4. Diffusivity measures of the inferior fronto-occipital fasciculus of the schizophrenia spectrum disorders patients and healthy control subjects of both samples.

	Bern sample (Schizophrenia; n = 89)					Basel sample (First episode psychosis; n = 48)				
	Patients (n = 45)		Controls (n = 44)			Patients (n = 24)		Controls (n = 24)		
Tract (measure)	**Mean**	**SD**	**Mean**	**SD**	**Effect***	**Mean**	**SD**	**Mean**	**SD**	**Effect***
Left IFOF										
FA (0-1)	0.506	0.027	0.511	0.020	Con>Pat	0.459	0.031	0.465	0.015	Con>Pat
AD (mm^2/s)	0.001224	0.000035	0.001218	0.000032	Pat>Con	0.001251	0.000055	0.001246	0.000033	Pat>Con
RD (mm^2/s)	0.000527	0.000042	0.000519	0.000022	Pat>Con	0.000603	0.000065	0.000589	0.000030	Pat>Con
MD (mm^2/s)	0.000759	0.000037	0.000752	0.000021	Pat>Con	0.000818	0.000059	0.000808	0.000030	Pat>Con
Right IFOF										
FA (0-1)	0.495	0.027	0.497	0.020	Con>Pat	0.462	0.028	0.460	0.013	Pat>Con
AD (mm^2/s)	0.001244	0.000044	0.001239	0.000031	Pat>Con	0.001269	0.000038	0.001274	0.000040	Con>Pat
RD (mm^2/s)	0.000550	0.000049	0.000544	0.000028	Pat>Con	0.000608	0.000051	0.000614	0.000030	Con>Pat
MD (mm^2/s)	0.000781	0.000045	0.000775	0.000025	Pat>Con	0.000829	0.000043	0.000834	0.000032	Con>Pat

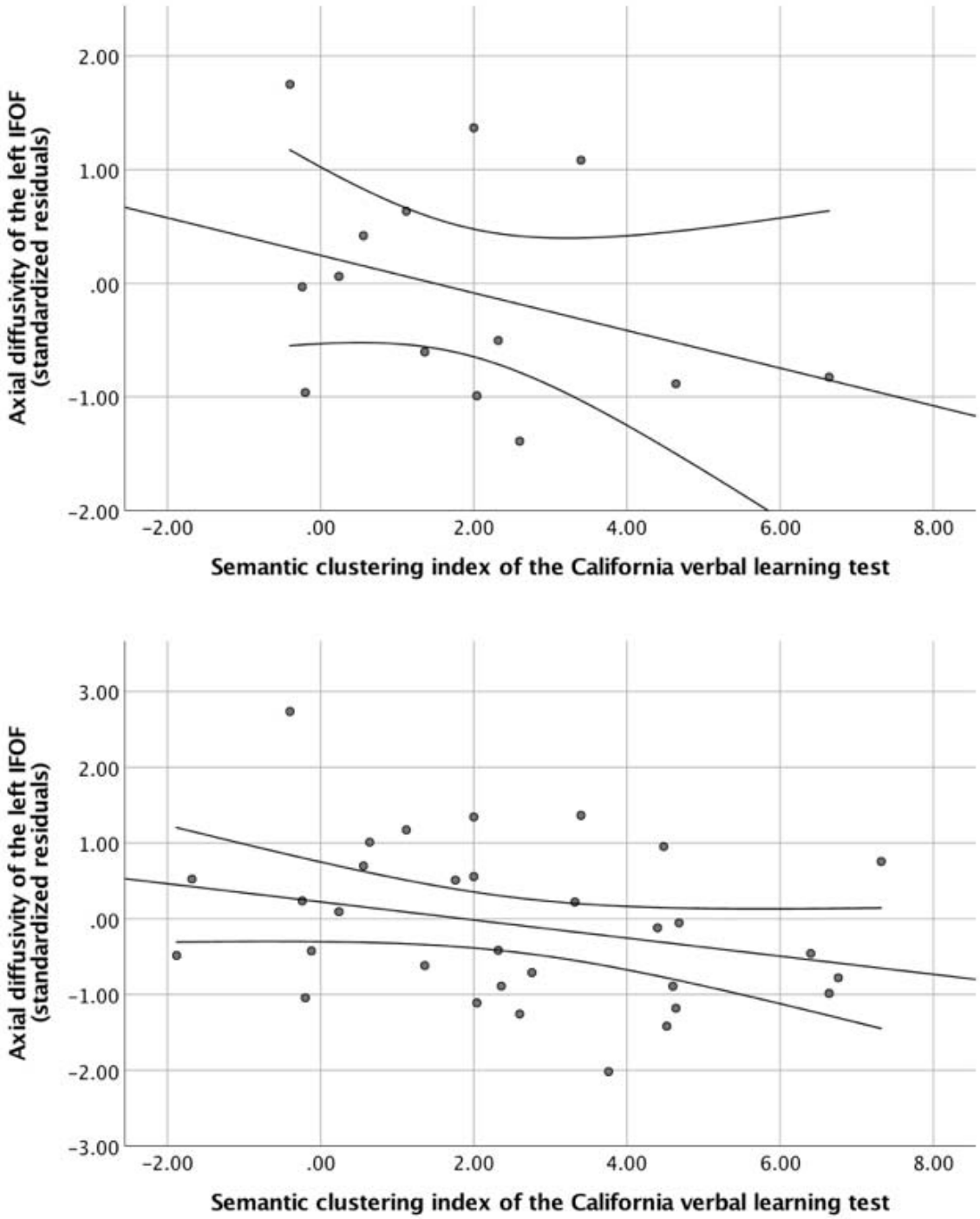
*Effect indicated the direction of diffusivity differences between groups, but does not urgently imply statistical significance for each single measure. However, the multivariate analyses for the left IFOF revealed statistically significant effects in both samples when considering all diffusivity measures simultaneously. Abbreviations: AD, axial diffusivity; Con, controls; FA, fractional anisotropy; IFOF, inferior fronto-occipital fasciculus; MD, mean diffusivity; mm, millimeter; n, number of participants; Pat, patients; RD, radial diffusivity; s, second; SD, standard deviation.

Supplementary Table 5. Correlations between semantic processing impairments and measures of tract integrity within the schizophrenia spectrum disorders patients of the Basel sample.

		Fractional anisotropy	Axial diffusivity	Radial diffusivity	Mean diffusivity
IFOF left[A]	**Spearman's rho**	-0.332	**-0.376**	0.090	-0.081
	p-value	0.25	**0.185**	0.76	0.78
IFOF right[A]	**Spearman's rho**	-0.156	-0.099	0.196	0.073
	p-value	0.59	0.74	0.50	0.81
IFOF left[B]	**Spearman's rho**	0.081	**-0.317**	-0.230	-0.271
	p-value	0.66	**0.077**	0.21	0.13
IFOF right[B]	**Spearman's rho**	-0.030	-0.192	-0.092	-0.104
	p-value	0.87	0.29	0.62	0.57

[A], based only on 14 first episode psychosis (FEP) patients. There were no significant correlations at all most probably due to the small sample size. However, when using one-tailed hypothesis testing due to the known direction of the effect (as shown in the Bern sample), the inverse correlation between the list-based semantic clustering index (LBC) derived from the California verbal learning test (CVLT) and axial diffusivity of the left IFOF showed a trend towards significance ($r = -0.376$, $p = 0.0925$, one-tailed).

[B], based on 14 FEP patients and 18 healthy control subjects. There was a significant inverse correlation ($r = -0.317$, $p = 0.0385$, one-tailed) between axial diffusivity of the left IFOF and semantic impairments. Abbreviations: IFOF, inferior fronto-occipital fasciculus.



Supplementary Figure 1. Associations between semantic processing impairments and axial diffusivity of the inferior fronto-occipital fasciculus (IFOF).
Shown are the scatterplots of the correlations between semantic processing impairments and the axial diffusivity standardized residuals (after regressing out global axial diffusivity) of the left IFOF. This correlation has been computed across 14 first episode psychosis (FEP) patients only (upper panel) as well as across 14 FEP patients and 18 healthy control subjects (lower panel). Shown are the fitted regression line and the 95% confidence intervals. Note that the there was only a trend towards significance in the upper panel ($r = -0.376$, $p = 0.0925$, one-tailed), whereas the correlation reached statistical significance in the lower panel ($r = -0.317$, $p = 0.0385$, one-tailed).

SUPPLEMENTARY REFERENCES

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